“CBER 101”
An Introduction to the Center for Biologics Evaluation and Research (CBER)

Overview of the Office of Vaccines Research and Review (OVRR)

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Special Assistant, OVRR

OVRR Organization

- Immediate Office
  - Karen Midthun, M.D., Director
  - William Egan, Ph.D., Deputy Director
  - Norman Baylor, Ph.D., Associate Director for Regulatory Policy
  - Bette Goldman, Special Asst.

OVRR Organization
(continued)

- Division of Bacterial, Parasitic & Allergenic Products
  - Richard Walker, Ph.D., Director
  - Milan Blake, Ph.D., Deputy Director
- Division of Viral Products
  - Jerry Weir, Ph.D., Director
  - Philip Krause, M.D., Deputy Director
- Division of Vaccines & Related Products Applications
  - Karen Goldenthal, M.D., Director
  - Donna Chandler, Ph.D., Deputy Director

OVRR Mission

- Assure the safety, efficacy, purity, and potency of vaccines and related biological products

- Regulation of vaccines and allergenic products
  - Preventive vaccines
  - Certain therapeutic vaccines, especially for infectious disease indications
  - Toxins
  - Allergenic products

Vaccine Safety Issues

- **ADDITIVES IN VACCINES (e.g., thimerosal)**
- **AUTISM**
- **CANCER AND SV40**
- **BOVINE SPONGIFORM ENCEPHALOPATHY (BSE)**

Regulation of Vaccines and Related Products

- Review of Investigational New Drug Applications (INDs) and Biological License Applications (BLAs)
- Research related to development, manufacture and testing of vaccines and related products

Regulation of Vaccines and Related Products (continued)

- Lot-release testing of licensed products
- Inspections of manufacturing facilities
- Surveillance
- Compliance activities
- Policy development

OVRR Role in Regulatory Review and Approval

Pre-IND	IND	License
•Meeting with sponsors to provide guidance	•Eval. Assays to measure clinical response to prod.	•Present prod. To Advisory Comm.
•Tech. Advice for product and assay development	•Eval. product characterization methods & assays	•Rev. of final prod. manuf. process, in-cluding in process & final product specs.
	• Rev of orig. submission & all subsequent amendments	•Est. lot release protocols for CBER product Release
	•Rev. product manuf. data & determin-ation of prod. specs.	•Conduct pre-approval inspection of the Facility
		•Meet with sponsors

OVRR Role in Regulatory Review and Approval

Pre-IND IND License Post Licensure

- Review of Biological Deviation reports from industry
- Participation in biannual inspections of licensed products
- Review of post approval commitments
- Review of subsequent supplements for changes in manufacturing process or additional clinical indications
- Meet with sponsors

Selection of Guidance Information for Vaccine Development

- Guidance for Industry:Content and Format of CMC Information and Establishment Description Information for a Vaccine or Related Product 1/99
- Guidance for Industry for the Evaluation of Combination Vaccines for Preventable Diseases; Production, Testing and Clinical Studies 4/97
- Guidance:Considerations for Repro Tox Studies for Preventive Vaccines for ID Indications 9/00

Guidance (cont.)

- PTC on Plasmid DNA Vaccines for Preventive Infectious Disease Indications 12/96

- http://www.fda.gov/cber/vaccines.htm

PRODUCTION AND QUALITY CONTROL

IMPORTANCE OF:

- **Detailed manufacturing procedures:**
- **Defined compatible components**
- **Consistency of Production**
- **In Process Tests for Product Quality/Safety**
  - **viral yields, inactivation validation, amino acid analysis**
- **Source and quality of starting materials**

PRODUCTION AND QUALITY CONTROL (CONTINUED)

- Product characterization
  - specifications with defined ranges
- Cell substrates
- Purification: reagents, pyrogens, contaminants
  - validation of removal of testing or testing of residual levels in final product
  - adventitious agent testing
- Examination of extraneous materials
- Knowledge of stability
- Facility inspection

Division of Vaccines and Related Products Applications

- Vaccines Clinical Trials Branch
- Bacterial Vaccines and Allergenics Branch
- Viral Vaccines Branch

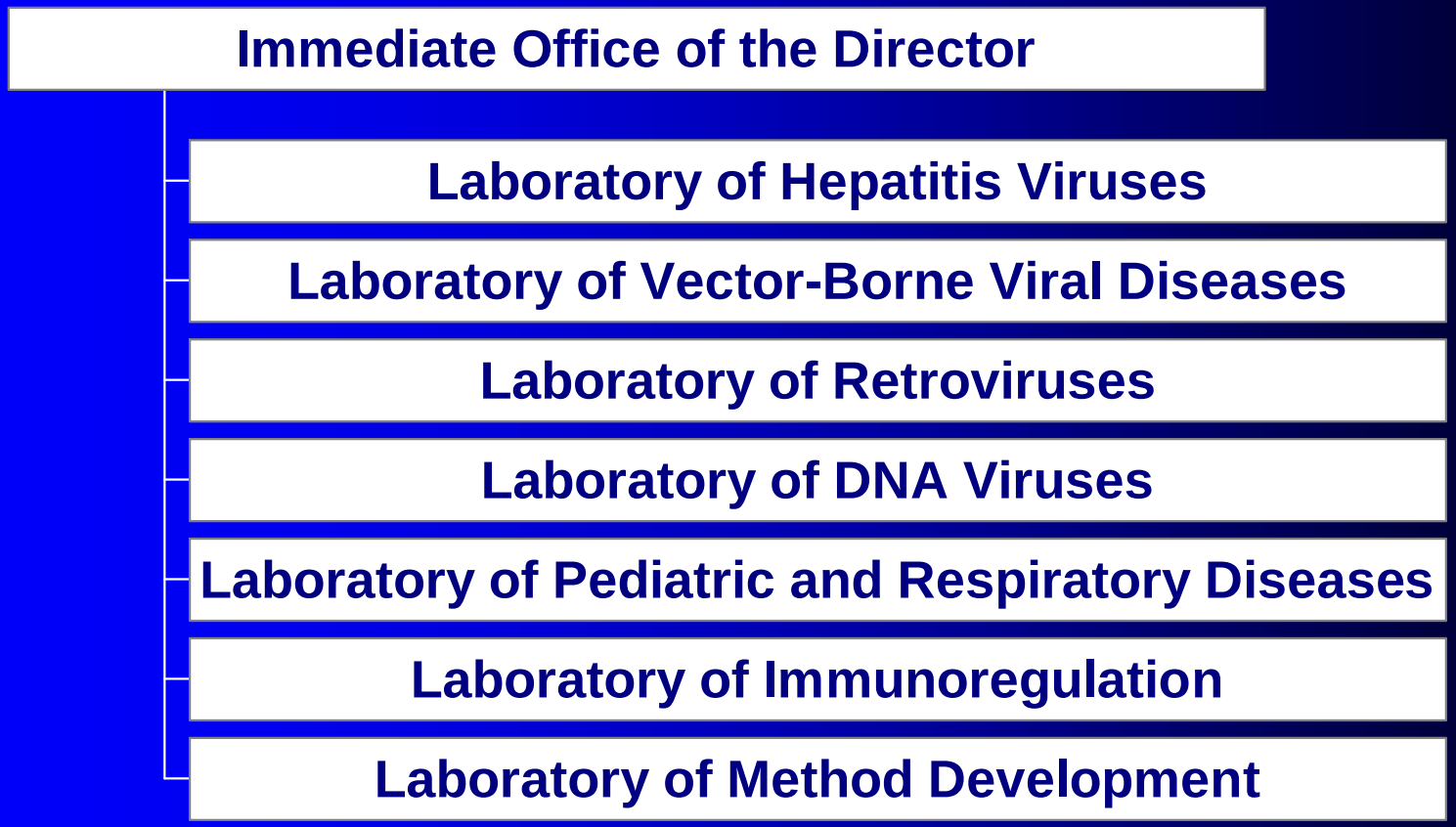
Division of Vaccines and Related Products Applications (DVRPA)

- Responsible for the receipt and administrative processing of biological Investigational New Drug applications (INDs) and Biologics License Applications (BLAs)

Division of Vaccines and Related Products Applications (DVRPA)

- Shares the responsibility with the laboratory-based divisions for the review of vaccines and related products regulated in OVRR (e.g.,viral, bacterial, rickettsial and parasitic vaccines; certain tumor vaccines; toxins; toxoids; diagnostic substances for dermal tests; venoms; and allergenic extracts.)

Division of Viral Products
Office of Vaccines Research and Review



Division of Viral Products Mission and Functions

- Research
  - Viral pathogenesis
  - Vaccine development & evaluation
  - Viral vector evaluation
  - Vaccine safety and efficacy

Division of Viral Products Mission and Functions

- Review
  - IND
  - BLA
  - Lot release
  - Post-marketing activities

EXAMPLES OF LICENSED VIRAL VACCINES

Inactivated

- Hepatitis A
- Hepatitis B, recombinant
- Influenza
- Japanese Encephalitis
- Poliovirus
- Rabies

Live

- Measles, Mumps and Rubella
- Poliovirus Oral, Trivalent
- Varicella
- Yellow Fever

Laboratory of Hepatitis Viruses

- **Research efforts**
  - **Immunobiology of hepatitis C**
  - **Strategies for vaccine development**

- **Major regulatory Responsibilities**
  - **Regulation of hepatitis virus A, B, and C vaccines**

Laboratory of Retrovirus Research

- **Major regulatory responsibilities**
  - **Regulation of HIV vaccines, cell substrates, and DNA vaccines**

- **Research efforts**
  - **Safety and immunogenicity of DNA vaccines and immunomodulatory CpG oligonucleotides**
  - **Retroviral tropism**
  - **Function of retroviral proteins**
  - **Retrovirus entry into cells**

Laboratory of DNA Viruses

- Research efforts
  - Poxvirus replication
  - Herpes virus gene expression
  - Viral latency
  - Detection of adventitious agents

Laboratory of DNA Viruses

- Major regulatory responsibilities
  - Regulation of herpes virus vaccines, poxvirus vaccines, and vaccine cell substrates

Laboratory of Pediatric and Respiratory Viral Diseases

- Research efforts
  - Neurovirulence safety test development
  - Role of host factors in viral pathogenesis and vaccine adverse reactions
  - Antigenic structure of RSV glycoproteins
  - Standardization and development of influenza virus vaccines

Laboratory of Pediatric and Respiratory Viral Diseases

- Major regulatory responsibilities
  - Regulation of influenza, measles, mumps, rubella, RSV, and other respiratory viral vaccines

Laboratory of Methods Development

- **Research efforts**
  - Development of assays for characterization of viral vaccine consistency and stability
  - Methods for evaluation of inactivated poliovirus vaccine
  - Development of methods for evaluation of cell substrates
  - Development of methods for virus detection

Laboratory of Methods Development

- Major regulatory responsibilities
  - Regulation of poliovirus vaccines

Division of Bacterial, Parasitic and Allergenic Products (DBPAP)

Laboratory of Respiratory and Special Pathogens

Laboratory of Immunobiochemistry

Laboratory of Bacterial Toxins

Immediate Office of the Director

Regulatory Staff
Administrative Staff

Laboratory of Biophysics

Laboratory of Mycobacterial Diseases & Cellular Immunology

Laboratory of Enteric & Sexually Transmitted Diseases

Laboratory of Methods Development and Quality Control

Laboratory of Bacterial Polysaccharides

Laboratory Mission and Functions

Assure Safe and Effective Products for Immunological Control of Bacterial, Parasitic and Allergenic Agents Affecting Human Health

Research

- **Review**
- **Post-licensure surveillance**
  - **Inspection/compliance**
  - **Lot release testing/protocol review**
  - **Label/promotional activity review**
- **Consultations with outside organizations**

EXAMPLES OF LICENSED BACTERIAL VACCINES

Inactivated

- Cholera
- Diphtheria & Tetanus Toxoids & Pertussis
- Haemophilus type b Conjugates
- Meningococcal Polysaccharide
- Pneumococcal Polysaccharide, and conjugate
- Typhoid
- Typhoid Vi Polysaccharide

Live

- BCG
- Typhoid, Ty21a, Oral

DBPAP Program Focus Areas

- Standardization of assay methods for bacterial, parasitic and allergenic substances
- Pertussis and other toxin-mediated diseases
- Mycobacterial and other intracellular parasites
- Mucosal pathogenesis and immunization
- Allergenic products and allergenic diseases
- Products to combat Bioterrorism agents

Laboratory of Methods Development and Quality Control

Areas of research

- Develop, standardize, and evaluate quality control methods for bacterial vaccines
- Develop, evaluate, and apply serological methods to measure immune response in vaccine trials
- Coordinate quality assurance activities within DBPAP
- Develop alternate potency assay for anthrax vaccines

Recent Milestones

- Developed QC methods incorporated into WHO acellular pertussis vaccine guidelines
- Leader in effort to standardize pertussis immunoassays of acellular pertussis vaccines

Laboratory of Bacterial Polysaccharides

Areas of Research

- Characterization of immune responses to polysaccharide and conjugate vaccines
- Standardization of methods for relevant clinical application
- Development of novel physical and chemical methods for improved evaluation of licensed and experimental vaccines
- Characterization of innovative approaches to vaccine development, and evaluation of epidemiologic aspects of vaccine candidates

Recent Milestones

- Licensure of pneumococcal conjugate vaccine
- Genetic typing method for gonococcal epidemiology
- Discovered conjugation modifies epitopes in polysaccharide vaccine conjugates

Laboratory of Respiratory and Special Pathogens

Areas of Research

- **Structure/Function Studies of Toxins**
- **Regulation of Virulence Factors of *B. pertussis* and *B. anthracis***
- **Animal Models of *B. pertussis* Infection**

Recent Milestones

• Led the effort to license acellular pertussis vaccines

Laboratory of Immunobiochemistry

Areas of Research

- **Allergen structure and function**
- **Immunomodulation of allergic responses**
- **Chemokines and chemokine receptors in the modulation of immune responses**

Recent Milestones

- **Development of a provisional US standard for latex**
- **Isolation and characterization of latex allergen Hev b 5**
- **Grass pollen allergen extract standardization**
- **Re-validation of competition ELISA to determine potency of grass & mite allergen extracts**
- **Statistical basis for assignment of release limits for standardized allergens**
- **Criteria for prioritization of allergens for standardization**

Bioterrorism Program

- Research/review for:
  - *B. anthracis*
  - *F. tularensis*
  - *Y. pestis*
  - Botulinum toxin
- Research areas:
  - Genetic manipulation and regulation
  - Virulence factors
  - Vaccine improvement
  - Immunologic assay standardization

New or Improved Products Possible

- Synthetic peptides (malaria)
- Nucleic acid (influenza)
- Viral and bacterial vectored (pox vectored & cholera vectored)
- Genetically engineered bacteria and viruses (M. TB and HIV deletions)
- Edible vaccines!

- On the horizon – HPV, meningococcal conjugate

Vaccines Of The Future

- Vaccines remain important tools for disease prevention.

- Advances in biotechnology are providing novel strategies to produce and deliver safer, and more effective vaccines for improving public health.

“Animal Efficacy Rule” 6/02

- Where human efficacy trials are not feasible or ethical
- Efficacy based on adequate and well-controlled animal trials if results establish that product reasonably likely to provide clinical benefit to humans
- Safety and pK (immunogenicity) data in humans still necessary
- To treat or prevent life threatening conditions caused by lethal or permanently disabling substances

Animal Efficacy Rule (cont.)

Must have

- Well understood pathophysiological mechanism for toxicity and its prevention by product
- Effect demonstrated in more than one animal species and expected to be predictive for human
- Animal endpoint clearly related to desired benefit in human
- Data on pK and pD in animals and humans understood to select effective dose in humans

Animal Efficacy Rule and Smallpox Vaccine

- Efficacy of new vaccines derived from strains with demonstrated efficacy based on comparison of take rates (vaccination scar) and immune responses with licensed vaccine in RCTs
- Efficacy of new vaccines derived from strains without demonstrated efficacy can be based on animal efficacy data (if scientifically appropriate) in addition to comparative human immune responses
- As for any biologic, licensure of new smallpox vaccine requires demonstration of safety, efficacy, quality and consistency of manufacturing

Enhancing the Public Trust in Vaccines Is a Partnership

- Food and Drug Administration
- Centers for Disease Control
- National Institutes of Health
- Department of Health and Human Services
- Health care provider organizations